Clinical trial results:
A double-blind, randomized investigator-initiated study to determine the safety and the effect of Diamyd® in combination with Vitamin D on the progression to type 1 diabetes in children with multiple islet cell autoantibodies

Summary

EudraCT number	2014-003755-64
Trial protocol	SE
Global end of trial date	07 October 2019

Results information

Result version number	v1 (current)
This version publication date	26 September 2020
First version publication date	26 September 2020

Trial information

Trial identification

Sponsor protocol code	DiAPREV/2014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02387164
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Skåne University Hospital
Sponsor organisation address	Jan Waldenströms gata 35, Malmö, Sweden, 20502
Public contact	Helena Elding Larsson, Skåne University Hospital, 46 040337676, helena.larsson@med.lu.se
Scientific contact	Helena Elding Larsson, Skåne University Hospital, 46 040337676, helena.larsson@med.lu.se

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2019
Global end of trial reached?	Yes
Global end of trial date	07 October 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate if Diamyd®, in children treated with relatively high dose vitamin D, may delay or stop the autoimmune process leading to clinical type 1 diabetes in children with ongoing persistent beta cell autoimmunity as indicated by multiple positive islet cell autoantibodies.

Protection of trial subjects:

After the injection of Diamyd/placebo at visits 1 and 2, each trial participant was to remain at the study clinic for at least 1 h and monitored by the study personnel. Additionally, the participants were offered to stay at the clinic for an additional 2h or contact the investigator by phone.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	24
Adolescents (12-17 years)	5
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was stopped prematurely after only 29 patients recruited and maximum 2 years follow up.

Pre-assignment

Screening details:

29 patients were screened and 26 entered the study

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ALUM-rhGAD65 + Vitamin D

Arm description:

Diamyd with Vitamin D supplementation

Arm type	Experimental
Investigational medicinal product name	Diamyd
Investigational medicinal product code	
Other name	ALUM-rhGAD65
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection of 20 microgram Diamyd 2 times with 1 month apart

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	Calciferol
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

2000 IE daily

Arm title	Placebo + Vitamin D

Arm description:

Placebo with vitamin D supplementation

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection 2 times with one month apart

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	Calciferol

Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

2000 IU daily

Number of subjects in period 1[1]	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D
Started	13	13
Completed	13	13

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 3 subjects dropped out after the screening visit before the randomization.

Period 2

Period 2 title	Treatment follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ALUM-rhGAD65 + Vitamin D

Arm description:

Diamyd with Vitamin D supplementation

Arm type	Experimental
Investigational medicinal product name	Diamyd
Investigational medicinal product code	
Other name	ALUM-rhGAD65
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection of 20 microgram Diamyd 2 times with 1 month apart

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	Calciferol
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

2000 IU daily

Arm title	Placebo + Vitamin D

Arm description:

Placebo plus Vitamin D supplementation

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection 2 times with 1 month apart

Investigational medicinal product name	Vitamin D
Investigational medicinal product code	
Other name	Calciferol
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

2000 IU daily

Number of subjects in period 2	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D
Started	13	13
Completed	10	11
Not completed	3	2
Lost to follow-up	2	-
Diagnosed	1	2

Baseline characteristics

Reporting groups	
Reporting group title	ALUM-rhGAD65 + Vitamin D
Reporting group description:	
Diamyd with Vitamin D supplementation	
Reporting group title	Placebo + Vitamin D
Reporting group description:	
Placebo with vitamin D supplementation	

Reporting group values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D	Total
Number of subjects	13	13	26
Age categorical Units: Subjects			
Children (2-11 years)	10	11	21
Adolescents (12-17 years)	3	2	5
Age continuous Units: years			
arithmetic mean	9	9.4	
standard deviation	± 2.89	± 2.73	-
Gender categorical Units: Subjects			
Female	7	4	11
Male	6	9	15
Celiac disease Units: Subjects			
No	11	13	24
Yes	2	0	2
Thyroid disease Units: Subjects			
No	13	13	26
Yes	0	0	0
Relatedness Units: Subjects			
First degree relative	4	2	6
General population	9	11	20
Weight Units: kilogram(s)			
arithmetic mean	33.7	36.6	
standard deviation	± 14.51	± 14.99	-

End points

End points reporting groups

Reporting group title	ALUM-rhGAD65 + Vitamin D
Reporting group description: Diamyd with Vitamin D supplementation	
Reporting group title	Placebo + Vitamin D
Reporting group description: Placebo with vitamin D supplementation	
Reporting group title	ALUM-rhGAD65 + Vitamin D
Reporting group description: Diamyd with Vitamin D supplementation	
Reporting group title	Placebo + Vitamin D
Reporting group description: Placebo plus Vitamin D supplementation	

Primary: Type 1 diabetes status month 24

End point title	Type 1 diabetes status month 24[1]
End point description: Number of subjects diagnosed with Type 1 diabetes at month 24	
End point type	Primary
End point timeframe: Month 24	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was interrupted prematurely when only 13 subjects were randomized to each treatment group. Only descriptive statistics were planned according to the SAP.

End point values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: Number of subjects				
Yes	1	2		
No	12	11		

Statistical analyses

No statistical analyses for this end point

Primary: Type 1 diabetes status overall

End point title	Type 1 diabetes status overall[2]
End point description: Number of subjects diagnosed with Type 1 diabetes overall in the study	
End point type	Primary

End point timeframe:

Over the entire study period including after month 24

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was interrupted prematurely when only 13 subjects were randomized to each treatment group. Only descriptive statistics were planned according to the SAP.

End point values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: Number of subjects				
Yes	2	2		
No	11	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Develompent of impaired glucose metabolism

End point title	Develompent of impaired glucose metabolism

End point description:

Number of subjects developing impaired glucose metabolism by month 18

End point type	Secondary

End point timeframe:

Month 18

End point values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: Number of subjects				
Yes	3	1		
No	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Progressive impaired glucose metabolism

End point title	Progressive impaired glucose metabolism

End point description:

Number of subjects with progressive impaired glucose metabolism at month 18

End point type	Secondary

End point timeframe:
Month 18

End point values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	4		
Units: Number of subjects				
Yes	1	0		
No	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Injection site reactions day 1

End point title	Injection site reactions day 1

End point description:
Number of subjects experiencing injection site reactions at Day 1

End point type	Secondary

End point timeframe:
Day 1

End point values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: Number of subjects				
Erythema	0	0		
Haematoma	0	0		
Itching	0	0		
Oedema	0	0		
Pain	0	0		
Tenderness	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Injection site reactions month 1

End point title	Injection site reactions month 1

End point description: Number of subjects experiencing injection site reacations	
End point type	Secondary
End point timeframe: Month 1	

End point values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: Number of subjects				
Erythema	1	0		
Haematoma	1	0		
Itching	0	0		
Oedema	2	0		
Pain	0	0		
Tenderness	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in GADA month 1

End point title	Change from baseline in GADA month 1
End point description: Change from baseline to month 1 in GADA titers	
End point type	Secondary
End point timeframe: Change from baseline to month 1	

End point values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: U/mL				
arithmetic mean (standard deviation)	1619.1 (± 2608.9)	-51.9 (± 197.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in GADA month 12

End point title	Change from baseline in GADA month 12

End point description:

Change from baseline to month 12 in GADA titers

End point type	Secondary

End point timeframe:

Change from baseline to month 12

End point values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: U/mL				
arithmetic mean (standard deviation)	7916.9 (± 10694.55)	-120.9 (± 592.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in GADA month 24

End point title	Change from baseline in GADA month 24

End point description:

Change from baseline to month 24 in GADA titers

End point type	Secondary

End point timeframe:

Change from baseline to month 24

End point values	ALUM-rhGAD65 + Vitamin D	Placebo + Vitamin D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: U/mL				
arithmetic mean (standard deviation)	3216.6 (± 4628.53)	1062.7 (± 3380.26)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From randomization up to 2 year follow-up or diagnosis of type 1 diabetes.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	ALUM-rhGAD65 + Vitamin D
Reporting group description: Diamyd with Vitamin D supplementation	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	ALUM-rhGAD65 + Vitamin D	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Post streptococcal glomerulonephritis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ALUM-rhGAD65 + Vitamin D	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	12 / 13 (92.31%)	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Upper limb fracture			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 13 (38.46%)	3 / 13 (23.08%)	
occurrences (all)	13	9	
Migraine			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 13 (30.77%)	5 / 13 (38.46%)	
occurrences (all)	6	11	
Pain			
subjects affected / exposed	2 / 13 (15.38%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injection site rash			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Vertigo			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 13 (23.08%)	2 / 13 (15.38%)	
occurrences (all)	3	2	
Abdominal pain upper			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Food poisoning			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	3 / 13 (23.08%)	1 / 13 (7.69%)	
occurrences (all)	3	2	
Cough			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Depression			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Insomnia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Growing pains			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 13 (76.92%)	9 / 13 (69.23%)	
occurrences (all)	49	20	
Ear infection			

subjects affected / exposed	3 / 13 (23.08%)	1 / 13 (7.69%)	
occurrences (all)	3	1	
Gastroenteritis			
subjects affected / exposed	3 / 13 (23.08%)	1 / 13 (7.69%)	
occurrences (all)	3	3	
Influenza			
subjects affected / exposed	2 / 13 (15.38%)	1 / 13 (7.69%)	
occurrences (all)	3	1	
Pharyngitis			
subjects affected / exposed	2 / 13 (15.38%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Otitis media			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Tooth infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Varicella			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Conjunctivitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Enterobiasis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Febrile infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Impetigo			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was stopped prematurely when only 26 out of 80 patients were recruited and followed for maximum 2 years rather than planned 5 years.

Notes: